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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: [Docket No. 2005D-0022] - **International Conference on Harmonisation; Draft Guidance on S8 Immunotoxicity Studies for Human Pharmaceuticals, Request for Comments**

Merck & Co., Inc. is a leading worldwide, human health products company. Through a combination of the best science and state-of-the-art medicine, Merck's Research and Development (R&D) pipeline has produced many important pharmaceutical products available today. These products have saved the lives of or improved the quality of life for millions of people globally.

Merck Research Laboratories (MRL), Merck's research division, is one of the leading biomedical research organizations. MRL tests many compounds as potential drug candidates through comprehensive, state-of-the-art R & D programs. Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment.

In the course of bringing Merck product candidates through developmental testing and clinical trials, Merck scientists address issues affected by this proposed Guidance. We have extensive experience in assessing parameters of immune function, and in conducting additional immunotoxicity studies to evaluate the significance of an effect of a new molecular entity on the immune system.

Merck commends the International Conference on Harmonization (ICH) for examining immunotoxicity studies for human pharmaceuticals. We support the recommendation that parameters examined in standard toxicity studies (STS) should be used to screen for immunosuppression and follow-up studies be performed only when a cause-for-concern has been identified through a weight-of-evidence review of relevant data. However, we are concerned that this draft guidance lacks clarity regarding (1) the exclusion of known immunomodulators, (2) the evidence of carcinogenicity as a trigger, (3) the recommendation to perform additional studies based on an overall review of the relevant data rather than on a single trigger, (4) the definition of the targeted patient population as a cause for concern, (5) the value of additional animals studies when follow-up immunotoxicity studies are included in the design of the clinical program, and (6) the

timing of immunotoxicity testing in relation to clinical studies. Our specific comments follow. We present each comment, referenced by section and line number, followed by our recommendation.

1) Section 1.3, *Scope of the Guideline,* Lines 101 to 114

Comment: The draft guidance fails to provide clarity regarding the exclusion of drugs for which immunomodulation is the pharmacological effect.

Recommendation:
Lines 113 to 114 in the guidance should be modified to read: "It is beyond the scope of this guidance to provide specific guidance on how each immunotoxicity study should be performed. General guidance is provided in Appendix 1. *Furthermore, drugs intended to induce immunomodulation are not within the scope of this guideline."*

2) Section 2.1.1, *Standard Toxicity Studies,* Line 158

Comment: The draft guidance identifies "Evidence of carcinogenicity, especially in the absence of genotoxicity" as a sign of immunotoxic potential. Merck agrees that carcinogenicity may in fact be an indication of immunosuppression. However, as is stated in the FDA guidance (2002)[1], "the relationship between immunosuppression and cancer is complicated and controversial. Under most circumstances, when increased incidence of tumors is observed in standard 2-year rodent bioassays (or in other nonclinical toxicology studies), this effect is likely related to genotoxicity, hormonal effects, or other relatively well understood mechanisms. However, for some investigational drugs the cause of tumor findings in nonclinical studies might not be apparent."

Recommendation:
Line 158 in the listing of possible signs of immunotoxic potential should be modified to reflect the FDA guidance noted above: "(5) Evidence of carcinogenicity, especially in the absence of genotoxicity. *Under most circumstances, when increased incidence of tumors is observed in standard rodent bioassays, this effect is likely related to genotoxicity, hormonal effects, liver enzyme induction, hyperplasia, or other relatively well understood mechanisms. However, for some investigational drugs the cause of tumor findings in nonclinical studies might not be apparent. In cases where a potential role of immunosuppression is plausible based on a weight-of-evidence review of the relevant data, functional assays should be considered."*

3) Section 2.1.1, *Standard Toxicity Studies,* Lines 160 to 162 and Section 2.1.2 *Other Causes for Concern in the Weight-of-Evidence Review,* Lines 204 to 206

[1] Guidance for Industry. Immunotoxicology evaluation of investigational new drugs. FDA CDER. October 2002.

Comment: The draft guidance lacks clarity regarding the decision to perform additional studies based on an overall review of the relevant data rather than on observance of a single trigger.

Recommendation:
Lines 160 to 162 in the guidance should be modified to read: "If the findings from the STS indicate that there are signs of immunotoxicity, the decision to conduct additional immunotoxicity testing should be considered in a weight-of-evidence review of the data *and not based only on a single trigger from the list in 2.1.1 above.*"

Lines 204 to 206 of the guidance should be edited as follows: from "If signs of immunotoxicity are observed in STS and/or one of the above four factors apply, it is recommended that the sponsor conduct studies of drug effect on immune function or provide justification for not performing these evaluations" to "If signs of immunotoxicity are observed in STS *only or in conjunction with one of the four factors listed above* it is recommended that the sponsor conduct studies of drug effect on immune function or provide justification for not performing the evaluations."

4) Section 2.1.2, *Other Causes for Concern in the Weight-of-Evidence Review*, Lines 193 to 195

Comment: This draft guidance lists the "targeted patient population" as a cause for concern in the weight-of-evidence review but the definition of the targeted patient population is not clear. This statement refers to "immunocompromised" patients as an example but there is no clear definition of which populations would trigger additional testing. Therefore it is possible to interpret this category to include other populations such as children and the elderly.

Recommendation:
Lines 193 to 195 of the guidance should be modified to read: "The targeted patient population should also be considered *if the immune system of the majority of the patient population for whom the investigational drug is intended is compromised by a disease state or other therapy. However, in such cases, the potential immunosuppressive effect of a drug would be best addressed during the carefully-controlled clinical trials in the relevant target population. A functional assay for immunosuppression in animals is not considered valuable for addressing this particular concern, unless the weight-of-evidence review indicates the need for follow-up testing.* ~~For instance, additional immunotoxicity testing might be needed if the majority of the targeted patient population is immunocompromised.~~"

5) Section 3, *Follow-up Immunotoxicity Studies*, Lines 245 to 255

Comment: The draft guidance lacks clarity regarding the value of additional animal studies when follow-up immunotoxicity studies are included in the design of the clinical program. Some clinical programs are designed to include immunotoxicity testing,

regardless of a finding in the STS that would indicate the need for follow-up testing. For example, clinical trials conducted in programs where the drug is expected to induce immunotoxicity will likely plan to add immunotoxicity testing to the clinical protocol. In this case, additional functional assays in animals are of limited value.

Recommendation:
Line 252 to 255 of the guidance should be modified to read: "In situations where the development candidate might have a pharmacological effect on the immune system, that specific component or associated function could be monitored. *However, if immunotoxicity testing is included in the design of the clinical program (e.g., due to the targeted patient population and/or known effects of the investigational drug), follow-up preclinical immunotoxicity testing may not be required regardless of findings in the STS.* Additional guidance is beyond the scope of this guideline."

6) Section 4, *Timing of Immunotoxicity Testing in Relation to Clinical Studies*, Lines 259 to 261

Comment: The draft guidance lacks clarity regarding the timing of immunotoxicity testing in relation to clinical studies. Depending on the specific clinical program, "a large population" is typically included in Phase III clinical trials.

Recommendation:
Lines 259 to 261 of the guidance should be modified to read: "If the weight-of-evidence review indicates the need for additional immunotoxicity studies, these should be completed *prior to Phase III clinical studies.* ~~before exposure of a large population of patients to the drug~~."

Conclusion
In summary, we support the recommendation that the parameters examined in standard toxicity studies should be used to screen for immunosuppression and a follow-up study be performed only when a cause-for-concern has been identified through a weight-of-evidence review of relevant data.

Although the guidance reflects an appropriate combination of the FDA guidance and the CHMP guidance[2] currently available for review, there are several issues which we feel require further clarification. These issues include (1) the exclusion of known immunomodulators, (2) the evidence of carcinogenicity as a trigger, (3) the recommendation to perform additional studies based on an overall review of the relevant data rather than on a single trigger, (4) the definition of the targeted patient population as a cause for concern, (5) the value of additional animals studies when follow-up immunotoxicity studies are included in the design of the clinical program, and (6) the timing of immunotoxicity testing in relation to clinical studies. To address the need for

[2] Note for guidance on repeated dose toxicity. EMEA/CPMP 2000.

further clarification of these points, we recommend the guidance be revised as noted herein.

We appreciate the opportunity to share our comments with respect to the ICH Draft Guidance on S8 Immunotoxicity Studies for Human Pharmaceuticals. Please do not hesitate to contact me, should you have any questions.

Sincerely,

Taryn Rogalski-Salter, PhD
Director
Regulatory Policy